IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	IL HWAN CHO, ET AL.	Group Art Unit: 1625
Serial No.:	10/608,709	
Filed:	JUNE 27, 2003	Examiner: Morris, Patricia L.
For:	1, 2, 4-TRIAZOLE DERIVATIVE, METHOD FOR PREPARING THE SAME, AND PHARMACEUTICAL COMPOSITION CONTAINING THE SAME	

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The inventor of the above-referenced application declares and says:

1. I, Cho, Il-hwan, declare and say that I am an inventor in US Patent Serial No. 10/608,709 (hereinafter "present application").

2. I, Cho, Il-hwan received a Bachelor's Degree in Chemistry from Sungkyunkwan University in 1983, and received a Master's Degree in Chemistry from Sungkyunkwan University in 1985. I have been employed by CJ corp., 500 Namdaemunro 5-ga, Jung-gu, Seoul, Republic of Korea, for about 16 years. During that period of time I have been engaged in a research program in the field of drug discovery, in the area of organic chemistry.

3. I have reviewed and understand the references: EP 1099695 to Pascal et al. (hereinafter "Pascal") and US 2003/0125368 to Sakya et al. (hereinafter "Sakya").

4. Pascal teaches 5-aryl-1H-1,2,4-triazole compounds as inhibitors of cyclooxygenase-2 and pharmaceutical compositions containing them. Sakya teaches sulfonyl-aryl triazoles as anti-inflammatory/analgesic agents.

5. I tested the COX-2 inhibition % of the compounds of Pascal and the compounds of the present application, respectively. The compounds as disclosed in Examples 17 and 18 of the Pascal were tested and compared with the compounds as disclosed in Examples 27, 28 and 35 of the present application, with respect to the COX-2 inhibition %. The test was conducted according to the method disclosed on pages 72-75 of the present application.

6. Table A: COX-2 inhibition % of the compounds of Pascal and the compounds of the present application.

Compound of Pascal			Compound of the present application		
Example Nos.	% inhibition of COX-2 (10nM)	% inhibition of COX-2 (100nM)	Example Nos.	% inhibition of COX-2 (10nM)	% inhibition of COX-2 (100nM)
17	11.02	18.33	28	28.62	73.32
18	8.56	26.72	27	16.04	71.06
			35	38.65	82.56

The compounds as disclosed in the Examples 18 and 17 of Pascal were the position isomers of the compounds as disclosed in the Examples 27 and 28 of the present application, respectively. The compounds as disclosed in the Examples 27 and 28 of the present application showed superior property in inhibiting COX-2 in comparison of the compounds as disclosed in the Examples 18 and 17 of Pascal, as shown in Table 1. In view of the fact that a pharmaceutical effect, for example, an anti-inflammatory effect, depends on the inhibition activities of COX-2, the compound of the present application, showed a higher activity in inhibiting COX-2 than the compound of Pascal did, is unexpectedly superior in treating the anti-inflammatory, in comparison with the compound of Pascal.

7. I tested the selectivity for inhibiting COX-2 over COX-1 of the compounds of Sakya and the compounds of the present invention, respectively, according to the method disclosed on pages 72-75 of the present application. The

compounds as disclosed in Examples 1, 2, and 4 of Sakya, which had aminosulfonylphenyl at the 1st positions of 1,2,4-triazole moiety, were prepared and tested with respect to the selectivity for inhibiting COX-2 over COX-1. The compounds as disclosed in Examples 25, 29, and 41 of the present application, which had methanesulfonylphenyl at the 1st positions of 1,2,4-triazolo moiety, were prepared and tested with respect to the selectivity for inhibiting COX-2 over COX-1.

8. Table 2: Selectivity for inhibiting COX-2 over COX-1

Compound of Sakya			Compound of the present application		
Example Nos.	% inhibition of COX-2 (10nM)	Selectivity	Example Nos.	% inhibition of COX-2 (10nM)	Selectivity
Example 1	18.31	23	Example25	7.62	460
Example 4	11.51	56	Example29	6.23	510
Example 2	4.22	32	Example41	8.88	390

In Table 2, the selectivity indicated that COX-1 (IC_{50})/COX-2 (IC_{50}). As shown in Table 2, the selectivity for inhibiting COX-2 over COX-1 of the compounds of the present application were significantly higher than that of the compounds of Sakya. Thus, the compound of the present application possesses unexpectedly superior in the selective inhibition of COX-2 to COX-1, in comparison of the compounds of Sakya.

9. I tested COX-1 and COX-2 inhibition for further compounds of the present application, according to the method disclosed on pages 73-75 of the present application. Table 3 showed the results.

10. Table 3: Cyclooxygenase (COX) Inhibition (%)

Samples	COX-1 (1 μ M)	COX-2 (10 nM)
Reference (Valdecoxib)	28.8	5.47
Example 25	29.2	7.62
Example 26	38.8	10.53
Example 27	13.8	16.04
Example 28	10.1	28.62
Example 29	16.7	6.23
Example 31	16.5	5.66
Example 32	19.9	12.6
Example 33	19.2	19.23

Example 34	23.5	26.82
Example 35	11.8	38.65

As shown in Table 3, the inhibition (%) ratios of COX-2 to COX-1 of the compounds of Examples 25-29 and 31-35 were significantly higher than that of the reference Valdecoxib. Thus, the compounds of the present application showed unexpectedly superior in the selective inhibition of COX-2 to COX-1, which is enough to rebut a prima facie case of obviousness.

11. Therefore, as shown in Tables 1-3, it is established that the compound of the present application has unexpected or unobvious properties in inhibition of COX-2 or selective inhibition of COX-2 to COX-1 vis-à-vis the compounds of Pascal or Sakya.

12. I declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or document or any patent resulting therefrom.

Date: 29 June 2005

IL HWAN CHO

Cho, Il-hwan